## Neonatal Necrotizing Enterocolitis

### Therapeutic Decisions Based upon Clinical Staging

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A method of clinical staging for infants with necrotizing entero-colitis (NEC) is proposed. On the basis of assigned stage at the time of diagnosis, 48 infants were treated with graded intervention. For Stage I infants, vigorous diagnostic and supportive measures are appropriate. Stage II infants are treated medically, including parenteral and gavage aminoglycoside anti-biotic, and Stage III patients require operation. All Stage I patients survived, and 32 of 38 Stage II and III patients (85%) survived the acute episode of NEC. Bacteriologic evaluation of the gastrointestinal microflora in these neonates has revealed a wide range of enteric organisms including anaerobes. Enteric organisms were cultured from the blood of four infants dying of NEC. Sequential cultures of enteric organisms reveal an alteration of flora during gavage antibiotic therapy. These studies support the use of combination antimicrobial therapy in the treatment of infants with NEC.

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A FTER A DECADE OF STUDY, the precise etiology and pathophysiology of neonatal necrotizing en-tercolitis (NEC) remain unclear. Numerous reports implicating various factors and perinatal influences have been presented.[1,2,4,6,13,16,18,26,27] At the present time, no proven preventive measures have been de-veloped, although one study suggests that prophylactic use of kanamycin in feedings may decrease the inci-dence of the disease.[10] Current practice emphasizes early recognition and vigorous efforts to minimize the impact of the illness.

Necrotizing enterocolitis can be recognized at vari-ous stages; a spectrum exists between a fulminant form, progressing to intestinal necrosis in 12–24 hours, and a more slowly evolving and benign form.[15,17] In fact, in its earliest stages NEC may resemble a number of other conditions prevalent in the neonatal population.

Comparison of the results of various treatment pro-grams for NEC is hampered by the lack of a uniformly accepted set of diagnostic criteria and failure to deline-ate precisely the stage of the disease at the time of diag-nosis. In the study to be described, a simple classifica-tion system has been applied in an effort to effect uni-formity in the therapeutic decisions which have been made in the management of these infants.

### Materials and Methods

The study group was derived from the newborn pop-ulation hospitalized at St. Louis Children's Hospital Neonatal Intensive Care Unit and the nurseries of Barnes Hospital. Between 1968 and 1975, 97 patients were evaluated and treated for NEC. During an 18 month period from July, 1974 through December, 1975, 48 infants were classified and treated in a prospective fashion, and these infants form the basis of this report. One or more of the authors evaluated all infants at the time that the diagnosis of NEC was first entertained.

TABLE 1. *NEC Staging System Based upon Historical, Clinical and Radiographic Data*

**STAGE I (Suspect)**

a. Any one or more historical factors producing perinatal stress.
b. Systemic manifestations—temperature instability, lethargy, apnea, bradycardia.
c. Gastrointestinal manifestations—poor feeding, increasing pregavage residuals, emesis (may be bilious or test positive for occult blood) mild abdominal distension, occult blood may be present in stool (no fissure).
d. Abdominal radiographs show distension with mild ileus.

**STAGE II (Definite)**

a. Any one or more historical factors.
b. Above signs and symptoms plus persistent occult or gross gastrointestinal bleeding; marked abdominal distension.
c. Abdominal radiographs show significant intestinal distension with ileus; small bowel separation (edema in bowel wall or peritoneal fluid), unchanging or persistent "rigid" bowel loops, pneumatosis intestinalis, portal vein gas.

**STAGE III (Advanced)**

a. Any one or more historical factors.
b. Above signs and symptoms plus deterioration of vital signs, evidence of septic shock or marked gastrointestinal hemorrhage.
c. Abdominal radiographs may show pneumoperitoneum in addition to others listed in II c.

## Staging of NEC

The criteria utilized in this group for the diagnosis of NEC and for grading the severity of disease are summarized in Table 1.

*Stage I.* An infant with these features may be designated as a case of suspected NEC. In order to exclude other neonatal disorders studies including bacterial cultures, electrolyte analysis, scrutiny of maternal drug history, coagulation studies, and contrast studies of the gastrointestinal tract are required.

*Stage II.* Other patients may be recognized as having NEC with greater certainty. Unequivocal malfunction of the gastrointestinal tract is demonstrated clinically and by radiographic evaluation. Other disorders such as malrotation and volvulus and Hirschsprung's disease must be excluded. These patients are designated as definite cases of NEC.

*Stage III.* Patients in an advanced stage of disease demonstrate evidence of bowel necrosis, peritonitis and septic shock. However, a small group of infants with NEC may have a less severe clinical course but radiographic evaluation shows pneumoperitoneum.

## Description of Patients

The 48 patients in the study group are characterized in Table 2. Commercially prepared 20 calorie per ounce formula had been fed to 43 infants. Two had been fed 24 calorie formula,* one had had 13 calorie formula,

* Similac (Ross).

one only sterile water and one received no feedings prior to the onset of symptoms.

## Treatment

Patients were treated on the basis of the assigned grade of severity of NEC when the child was encountered.

*Stage I.* Evaluation of these suspect patients included cultures of blood, urine obtained by suprapubic bladder puncture, cerebrospinal fluid, stool and gastric aspirates. In addition, complete blood count, platelet count, blood gases and pH, serum electrolytes and glucose and blood urea nitrogen were obtained. Stool and gastric content were examined for the presence of blood. Feedings were discontinued and intravenous fluids provided. Nasogastric decompression with a #10 French sump tube to intermittent suction was initiated, and intravenous antibiotics, if not already in use, were

TABLE 2. *Characterization of Patients by Clinical Stage. Signs and Symptoms Expressed as a Per Cent*

|  | Stage | | |
| --- | --- | --- | --- |
|  | I | II | III |
| Number of patients | 10 | 33 | 5 |
| Sex | | | |
|   Male | 70 | 57 | 60 |
|   Female | 30 | 43 | 40 |
| Race | | | |
|   Caucasian | 50 | 36 | 60 |
|   Black | 50 | 64 | 40 |
| Gestational Age (wks) | | | |
|   Mean | 34 | 33 | 33 |
|   Range | 29–40 | 26–40 | 30–40 |
| Small for Gestational Age | 40 | 33 | 40 |
| Birthweight (gm) | | | |
|   Mean | 1780 | 1610 | 1680 |
|   Range | 1000–3660 | 780–3620 | 945–3180 |
| Perinatal History | | | |
|   Pulmonary disease | 40 | 80 | 60 |
|   Cardiopulmonary or Temp. instability | 50 | 36 | 20 |
|   Abnormalities of labor and delivery | 20 | 36 | 60 |
|   Multiple births | 40 | 27 | 20 |
|   Infection (Maternal or infant) | 30 | 25 | 60 |
|   Umbilical catheter or exchange | 30 | 33 | 40 |
| Signs and Symptoms | | | |
|   Abdominal distension | 60 | 66 | 100 |
|   Increased pregavage aspirate | 60 | 30 | 40 |
|   Emesis | 20 | 42 | 40 |
|   Gastrointestinal bleeding | 60 | 69 | 60 |
|   Lethargy, cardiopulmonary or temp. instability | 30 | 33 | 60 |
| Radiographic Findings | | | |
|   Ileus and distension | 100 | 42 | 80 |
|   Interloop thickening | 20 | 18 | 0 |
|   Pneumatosis intestinalis | 0 | 78 | 60 |
|   Portal vein gas | 0 | 9 | 0 |
|   Pneumoperitoneum | 0 | 0 | 60 |

started. The infants were observed carefully for signs of progression of disease. Abdominal films were obtained at least daily for several days.

*Stage II*. If a definite diagnosis of NEC was made the measures outlined above were initiated. In addition, an aminoglycoside antibiotic (kanamycin or gentamicin), was delivered topically to the gastrointestinal tract by means of intermittent nasogastric gavage. Abdominal radiographs, including a left lateral decubitus film, were obtained at six to eight hour intervals initially and less frequently when clinical and radiographic improvement was noted. Treatment was continued for 48 hours after resolution of all clinical and radiographic abnormalities. At that time, the nasogastric suction and the gavage antibiotic were discontinued and the child observed for a further 24 hours. Feedings with dilute glucose-casein-medium chain triglyceride* formula was then begun. Parenteral antibiotics were continued for 10–14 days from the onset of symptoms, presuming the presence of sepsis secondary to bacterial invasion of injured intestine. Occult blood was frequently present in the stool of these infants for one to two weeks after the acute episode. Serial serum aminoglycoside concentrations were measured at intervals during the course of therapy.

*Stage III*. Operative intervention was undertaken because of intestinal perforation, severe gastrointestinal hemorrhage, deterioration of vital signs, or failure to respond to the therapy outlined for patients in Stage II. Operative therapy included diversion with resection of gangrenous or perforated intestine. Peritoneal cultures and saline lavage of the peritoneal cavity were performed and a tube gastrostomy was placed.

## Antibiotic Therapy

Thirty-six of the 48 patients were receiving antibiotic therapy before the onset of NEC. Most commonly, combinations of a semisynthetic penicillin, generally ampicillin (150–200 mg/Kg/24h), and an aminoglycoside, usually kanamycin (15 mg/Kg/24h) had been used. In the earliest months of the study period, when the diagnosis of NEC was made, this combination was continued if already in use, and gavage therapy with kanamycin (30 mg/Kg/24h in six divided doses) was carried out in seven patients.

From December, 1974 through the conclusion of this study period, parenteral antibiotics were changed to clindamycin (30 mg/Kg/24h) and gentamicin (5–7.5 mg/Kg/24h). Gavage therapy with gentamicin (10–15 mg/Kg/24h in six divided doses) was provided in addition to the parenteral therapy for 25 patients. Gavage aminoglycoside treatment was continued for a period of three to five days (mean four days).

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* Pregestimil (Mead-Johnson).

Serum aminoglycoside concentrations were measured in 20 of the 33 patients classified as Stage II. They were not studied in the other groups. Aminoglycoside serum concentrations were measured by the method described by Smith, et al.[20] Samples were obtained during the second 24 hour period of gavage therapy before and 15–30 minutes after intravenous doses and before and one to two hours after gavage. Seventy-one individual serum determinations were performed, a mean of 3.5 determinations for each patient studied. Pretreatment concentrations were obtained in eight infants who were already on parenteral aminoglycosides at the time of diagnosis of NEC.

## Bacteriologic Studies

Blood, gastric and fecal cultures were processed for both aerobic and anaerobic organisms in most cases. Blood cultures were obtained at the time of initial evaluation of the patient for NEC from all ten Stage I patients, 32 of 33 Stage II patients, and four of five Stage III patients.

Before starting gavage antibiotic therapy, nasogastric aspirate and rectal swab for fecal culture were obtained. Initial gastric aspirate cultures were obtained from five of ten Stage I, 22 of 33 Stage II, and one of five Stage III patients. Initial stool cultures were obtained from six of ten Stage I patients, 20 of 33 Stage II patients, and three of five Stage III patients. Sequential stool and gastric culture studies were performed on one or two subsequent days during gavage antibiotic therapy in 13 patients.

## Operative Therapy

Operative procedures were performed on nine patients (19%) for indications of perforation in five, clinical deterioration in three and profuse lower gastrointestinal hemorrhage in one infant. Segmental resection of the most severely affected bowel, including the site of perforation, and proximal diversion with construction of a distal mucous fistula was performed in seven patients. Mikulicz enteroenterostomy at the site of perforation was performed in one patient. One child underwent only laparotomy at which time the entire colon and small bowel were found to be involved with NEC.

## Results

### Complications

Complications associated with NEC and its treatment were noted in ten infants who survived the acute phase of the illness. Intestinal strictures occurred in three patients after successful medical therapy. Operative relief of obstruction was required in all three; one

infant died. Another child required revision of a stenotic ileostomy stoma.

Four infants developed complications during treatment with total parenteral nutrition. A prolonged, but self limited, cholestatic process occurred in one infant. One child developed an unexplained hemolytic anemia. Right atrial thrombosis with microscopic pulmonary thromboembolism, and perforation of a catheter into the right hemithorax occurred in two other infants. Two infants had recurrent, but less severe episodes of NEC when feedings were resumed.

## Mortality

Among the 48 patients treated during this period, 36 survived and 12 died, a raw mortality rate of 25%. However, this figure requires further scrutiny. Since the Stage I patients may not have had NEC, or a very mild form of the disease, and all survived, one might focus on the 38 infants in Stages II and III. In that group mortality directly attributable to NEC may be derived from the following consideration. Of the 12 infants who died, five deaths occurred during the acute phase of NEC and one following a secondary obstructive episode. The remaining six infants died of severe pulmonary disease having recovered from NEC under the treatment program previously outlined. Pulmonary mortality was at an interval after recovery from NEC which suggests that NEC did not contribute to the ultimate demise of the patient. Therefore, the mortality attributable to NEC was six of 38, or 15%.

Retrospective examination of the clinical and cultural characteristics of the infants who died of NEC permits identification of the infants at greatest risk. There were three females, three males, three caucasian and three black. Weights ranged from 860 to 1540 grams with a mean weight of 1225 g. Four of six (67%) were small for gestational age, the gestational age ranging from 30 to 35 weeks. This contrasts with the surviving infants whose mean weight was 1810 g, and among whom only 27% were small for gestation age. Although suggestive, these differences are not statistically significant in this small series. Four of the six infants who died of NEC had positive blood cultures at the time of or immediately before the onset of symptoms. Among the 26 surviving infants, 22 had blood cultures obtained at the onset of NEC symptoms. Twenty had no growth and two were considered contaminated. The organisms grown from the blood of infants dying of NEC were all enteric organisms. Three of the six infants who expired had portal venous gas seen on radiographic examinations of the abdomen. Also characteristic of the infants who died of NEC was the rapidly progressive and virulent course which the disease followed both before and after operation. Prominent in these infants was the presence of disseminated intravascular coagulation and evidence of pulmonary and intracranial hemorrhage.

Thirty-three Stage II patients were treated initially as outlined previously, including gavage antibiotics in 32. Five of these infants (15%) developed progressive disease and advanced to Stage III status. Indications for operation were evidence of perforation in two, and rapid deterioration in three. Four of these infants died as a result of NEC. One Stage II infant, who survived the initial episode, died after developing an intestinal
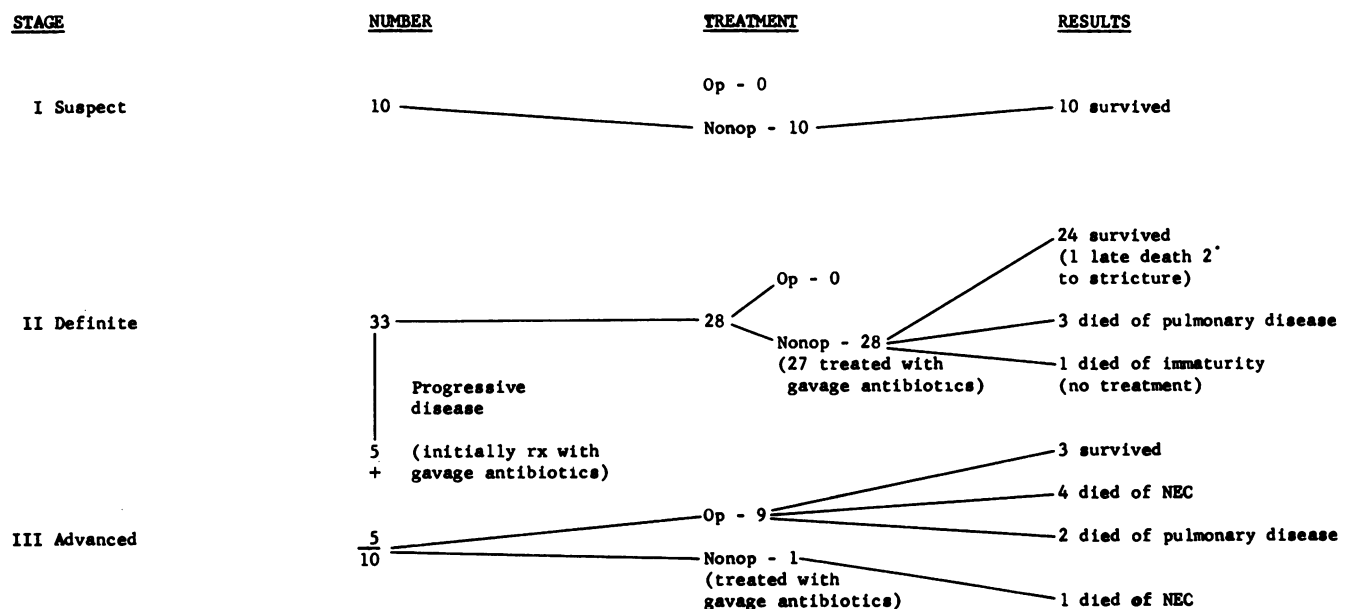


FIG. 1. Results of treatment.

stricture. Mortality for Stage II disease is therefore 15%.

Five infants initially were encountered at Stage III, of whom four underwent immediate laparotomy and two survived. Another child, who was treated inappropriately by non-operative means only, deteriorated rapidly and expired. Mortality for Stage III disease is therefore 60%. Of all the infants who ultimately satisfied the criteria for Stage III (ten), five (50%) died of NEC. These results are summarized in Figure 1.

### Bacteriology of NEC

*Blood cultures.* Blood samples obtained from all ten Stage I patients were sterile. Two of the blood cultures obtained in 32 of 33 Stage II patients were positive; one yielded *E. coli*, and the other *K. pneumoniae*. Both these children died of NEC. Blood cultures were positive in three patients in Stage III NEC. Organisms grown were *Peptostreptococcus*, gamma streptococcus and alpha streptococcus, *E. coli* and *Streptococcus agalactiae*. All three of these infants died, two of NEC.

*Gastric cultures.* The gastric aspirate from three of five Stage I patients were sterile. Gastric aspirate cultures from the two remaining patients grew gamma streptococcus, and *S. epidermidis*. The gastric aspirate cultures from eight of 22 stage II patients were sterile. The remaining 13 patients grew one or more organisms; these are listed in Table 3. Only one infant with Stage III disease had a gastric aspirate culture, which grew *E. coli*, *K. pneumoniae*, *Streptococcus agalactiae* and *S. epidermidis*.

*Stool cultures.* Cultures of stool were obtained from 38 patients. One was reported to have no growth. No pathogenic organisms were identified among stool cultures. Twenty-two patients had fecal culture studied to recover all organisms present. The organisms encountered in 32 patients of Stage II and III are listed in Table 3. Most patients had two or more organisms isolated, and seven (13%) anaerobic isolates were found among a total of 52 isolates.

Sequential fecal cultures were studied in 13 patients receiving gentamicin gavage. A change in the fecal microflora during the course of therapy was noted (Table 4). Most notable was the reduction in the number of gram negative species isolated and a relative increase in gram positive organisms and yeast.

*Serum aminoglycoside studies.* Serum concentration of aminoglycoside antibiotics was obtained in eight patients who already were receiving aminoglycoside therapy at the time of diagnosis of NEC. On four occasions the serum concentration of aminoglycosides was greater than the maximum serum concentration expected with the doses previously mentioned (10 yg/ml).

TABLE 3. *Gastric and Fecal Organisms Acquired from Stage II and III Patients (Number of Isolates)*

| Gastric Organisms | Number of Isolates | Fecal Organisms | Number of Isolates |
|---|---|---|---|
| S. epidermidis | 8 | S. epidermidis | 10 |
| S. aureus | 2 | S. aureus | 1 |
| Gamma streptococcus | 4 | Gp D strep | |
| K. pneumoniae | 8 | enterococcus | 4 |
| E. coli | 3 | S. agalactiae | 1 |
| citrobacter | 1 | K. pneumoniae | 10 |
| B. fragilis | 1 | E. coli | 15 |
| B. oralis | 1 | E. aerogenes | 1 |
| saccharomyces | 1 | citrobacter | 1 |
| | | corynebacterium | 1 |
| | | B. fragilis | 5 |
| | | Cl. perfringens | 1 |
| | | peptostreptoccus | 1 |
| | | Veillonella parvula | 1 |

All four patients were receiving kanamycin parenterally only, and the dosage schedules for kanamycin in all neonates have since been revised. Five of 71 serum specimens obtained from patients receiving combined gavage and intravenous gentamirin had concentrations above 10.0 yg/ml. All but one of these patients had other serum aminoglycoside concentrations in the usual therapeutic range.

### Discussion

During an 18 month period we have studied and treated 48 patients with NEC. An effort was made to assess the severity of the illness and to provide graded intervention based on that assessment. We have designated these stages in NEC as Stage I (Suspect), Stage II (Definite) and Stage III (Advanced). Infants who were classified Stage I were provided supportive care and intensive diagnostic evaluation was carried out to exclude other causes of their symptoms. Infants classified as Stage II were treated medically, with both parenteral and topical antibiotic therapy delivered by nasogastric gavage. Infants with Stage III disease required operative treatment. Use of this staging system will allow valid comparison of current and future efforts in the management of infants with NEC.

No patients who were considered suspect for NEC (Stage I) progressed to more advanced stages. While

TABLE 4. *Changes in the Fecal Microflora of Infants Treated with Aminoglycoside Gavage*

| | Culture #1 | Culture #2 | Culture #3 |
|---|---|---|---|
| Number of isolates | 29 | 31 | 20 |
| Gram negative isolates | 20 | 16 | 9 |
| Gram positive isolates | 9 | 14 | 7 |
| Anaerobic isolates | 4 | 3 | 3 |
| Yeast | 0 | 1 | 4 |

they may indeed have had early and mild NEC, easily aborted by simple means, they may not truly have had NEC. Clarification will require the development of a more specific method of early diagnosis. Hence they have been discarded from further evaluation of our therapeutic efforts.

The 85% survival of Stage II patients is encouraging; these results compare favorably to the mortality rates reported by others.[7,9,11,18,19,22,23,25] However, identification of infants first classified as Stage II who then progress to Stage III is a continuing challenge. Twenty-six of 33 Stage II patients demonstrated pneumatosis intestinalis, but only five of these advanced to Stage III. Three infants with portal vein gas were among this group. While this finding is ominous, other patients not included in this report have shown no progression of disease during non-operative therapy. Instability of vital signs, thrombocytopenia, metabolic acidosis, or persistent fixed distended loops of bowel all suggest progressive disease. Unfortunately, intestinal necrosis and perforation may have developed already when these signs appear. Even less encouraging are the results obtained in the infants with advanced disease who require surgical intervention. Some of these infants developed their symptoms and died within 12–18 hours. There appears to be no effective therapy currently available for this fulminant form of NEC.

Thirty-two patients received gavage aminoglycoside antibiotic therapy in addition to the other supportive care generally provided for infants with NEC. Several of these infants deteriorated rapidly after the initial evaluation, and two developed perforation. Twenty-four of these patients are alive and well at the time of this report with no obvious functional intestinal insufficiency or other abnormalities related to NEC.

The bacteriologic studies reported here support the use of a combination of antibiotics effective against the microflora usually resident in the gastrointestinal tract of these neonatal patients. A wide range of enteric organisms including anaerobes were found. Gastric aspirates contained an unusual distribution of enteric gram negative organisms and anaerobes in a number of patients. Blood cultures grew enteric organisms in four of six infants who died of NEC. Since patients with NEC may have an alteration in the bowel wall permitting entrance of microorganisms into the circulation, the use of antibiotics effective against the organisms usually present seems reasonable. In patients with evidence of perforation such therapy is mandatory. The studies of Weinstein and associates support the use of an aminoglycoside and clindamycin as the regimen which provided the most effective therapy for peritonitis.[28]

The precise role of the enteric microflora in the patho-physiology of NEC is unclear. There are several reports in which specific organisms have been implicated in patients with NEC.[11,12,18,21] Our data fail to support this possibility in our patients. However, other investigations have suggested that suppression of the enteric microflora might contribute to improvement in the results of treatment of NEC.[3,5] Preliminary evaluation of sequential enteric cultures in a small number of patients reveals a change in the microflora during the course of aminoglycoside gavage. A quantitative effect also may have been derived from this therapy but this was not evaluated in the current study. A control group for Stage II patients who receive no gavage aminoglycoside has not been included which makes assessment of this particular element of care impossible. This aspect of treatment deserves further study. Similarly, further evaluation of the gastrointestinal microflora in NEC is indicated. A comparison of the microflora of infants with NEC with normal term infants and other ill infants is in process.

It continues to be our impression that NEC is best treated by early, vigorous medical means, and that operative intervention should be reserved for those patients who fail to respond, or in whom complications supervene.

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